I. PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one-month to and including February 3, 2003, in which to file the instant response. Pursuant to 37 C.F.R. § 1.17, a check in the amount of $110.00 is enclosed, which is the process fee ($110.00) for a one-month extension of time. If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the instant response, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski L.L.P. Account No.: 50-1212/DEKM:157USC1/RH10056.

II. AMENDMENT

In the Specification:

Please replace the paragraph beginning at page 2, line 2, with the following:

D1

--This application is a continuation of Application Serial No. 08/927,368, filed September 11, 1997, now abandoned; which is a continuation-in-part of Application Serial No. 08/899,247, filed July 23, 1997, now abandoned; which is a continuation-in-part of Application Serial No. 08/832,078 filed April 3, 1997, now issued as U.S. Patent No. 6,040,497. --

Please replace the paragraph beginning at page 86, line 11, with the following:

D2

--Glyphosate resistant corn lines GA21, FI117, GG25 and GJ11 were crossed to various inbred lines to facilitate hybrid development as described in example 14. Genomic DNA used for Southern blot analyses was isolated from the resulting backcrossed plants. The backcross populations consisted of plants that were segregating 1:1 for the GA21, FI117, GG25 or GJ11 insertion. Positive and negative GA21 segregants were identified by polymerase chain reaction (PCR) using oligonucleotide primers specific to the pDPG434 fragment used for transformation. Negative segregants served as nontransgenic control plants. The PCR primers used for the analysis spanned the mutant EPSPS-nos junction and generated a 192 bp fragment. The sequence of the upper primer located on the mutant EPSPS gene is 5'-ACGTACGACGACCACAGGATG-3' (SEQ ID NO:1). The sequence of the lower primer located in nos is 5'-GCAAGACCGGCAACAGGATTC-3' (SEQ ID NO:2). Genomic DNA was isolated from positive and negative plants as described in Dellaporta *et al.*, (1983). DNA was isolated from field-grown and greenhouse-grown plants. --

Please replace the paragraph beginning at page 86, line 27, with the following:

--DNA fragments used for probe preparation were isolated by gel-purification of restriction digests of plasmid DNA or were generated by PCR. The mutant EPSPS PCR fragment used as a probe was generated using primers that produce a 324 bp fragment internal to the EPSPS gene. This fragment initiates approximately 400 bp down stream from the start codon. The primer sequences used to generate this fragment are: 5'-TTTGGCTCTTGGGGATGTG-3' (upper) (SEQ ID NO:3) and 5'-TTACGCTAGTCTCGGTCCAT-3' (lower) (SEQ ID NO:4). Probes were labeled with ^{32}P using the random priming method (Boehringer Mannheim) and purified using Quik-Sep® spin columns (Isolab Inc., Akron, OH). Blots were prehybridized at 65° C for 1-2 hours and hybridized with denatured probe for approximately 18 hours at 65° C. Prehybridization and hybridization solution consisted of 5X SCP, 2X Denhardt's Solution, 0.05 M Tris, pH 8.0, 0.2 % SDS, 10 mM EDTA, 100 mg/l dextran sulfate, and 125 µg/ml denatured salmon sperm DNA. Following hybridization, blots were washed 4 times for 10 min. in 0.25X SCP/0.2% SDS. Membranes were blotted dry and visualized by autoradiography. To reprobe blots, probes were removed by treating blots in 0.05 M NaOH/0.2% SDS for 10 min. followed by neutralization in 0.2 M Tris, pH 7.5/0.2% SDS/0.1 X SCP for 20 minutes at approximately 25° C. --

D3

Please replace the paragraph beginning at page 96, line 24, with the following:

--The presence of a gene in a transformed cell may be detected through the use of polymerase chain reaction (PCR). Using this technique specific fragments of DNA can be amplified and detected following agarose gel electrophoresis. For example the mutant EPSPS gene may be detected using PCR. Two hundred to 1000 ng genomic DNA is added to a reaction mix containing 10 mM Tris-HCl pH 8.3, 1.5 mM $MgCl_2$, 50 mM KCl, 0.1 mg/ml gelatin, 200µM each dATP, dCTP, dGTP, dTTP, 0.5µM each forward and reverse DNA primers, 20% glycerol, and 2.5 units Taq DNA polymerase. The primer sequences are (upper) 5'-TTTGGCTCTTGGGGATGTG-3' (SEQ ID NO:3) and (lower) 5'-TTACGCTAGTCTCGGTCCAT-3' (SEQ ID NO:4). The reaction is run in a thermal cycling machine as follows: 3 minutes at 94 C, 39 repeats of the cycle 1 minute at 94 C, 1 minute at 50 C, 30 seconds at 72 C, followed by 5 minutes at 72 C. Twenty µl of each reaction mix is run on a 3.5% NuSieve gel in TBE buffer (90 mM Tris-borate, 2 mM EDTA) at 50V for two to four hours. Using these primers a 324 base pair fragment of the mutant EPSPS transgene is amplified. --

D4

III. REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

A. Status of the Claims

Claims 84-87 and 96-99 were pending in the case at the time of the action and are presented herein for reconsideration.

B. Status of the Specification

The specification has been amended to insert sequence identification numbers and status information for the parent applications of the instant case as requested in the Action. It is believed that these issues are now moot in light of the amendments.

C. Status of the Information Disclosure Statement

The Action indicates that the IDS filed March 26, 2001 was non-compliant because a copy of the search report was not found in the parent application. In response, Applicants note that the reference was submitted in parent case Ser. No. 08/927,368 and was checked off as considered on January 19, 1999, by the Examiner in the parent case (Office Action mailed January 21, 1999). However, for the convenience of the Examiner, Applicants have attached a copy of the Search Report herewith as **Appendix C**.

D. Status of the Drawings

Submission of formal drawings has been requested. In response, Applicants note that formal drawings are being submitted herewith.

E. Rejections Under 35 U.S.C. §112, First Paragraph – Written Description

The action rejects claims 83-87 and 96-99 under 35 U.S.C. 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to convey to one of skill in the art that applicants were in possession of the claimed subject matter. In particular, it is alleged that applicants were not in possession of glyphosate-inducible male sterile plants other than events GG25 and GJ11. Applicants respectfully traverse.

Applicants first note that the claims are directed to a method of plant breeding, and not to corn plants that are capable of being rendered male-sterile by treatment with glyphosate. The relevant inquiry here is thus not whether written description has been established with respect to plants exhibiting glyphosate-inducible male sterility *per se*, but rather whether the claimed method has been adequately described to show possession of the invention. This has been fully done, as set forth below.

The rejection states that, although "Applicant describes maize lines GG25 and GJ11, comprising an EPSPS transgene that are capable of being rendered male-sterile by treatment of said lines with glyphosate," any other plant comprising an EPSPS transgene has not been described. Applicants note, however, that GG25 and GJ11 are transformation events, and not maize lines. As is described in the specification, these events may be transferred by plant breeding techniques into essentially any other maize plant. This, as well as procedures for introgression of a transgene into different maize plants are fully described in the specification. In Example 15, at pages 94-96 of the specification, also described are techniques for marker assisted breeding of EPSPS transgenes that may be used for such introgression.

The working Examples provide further description of the invention. In Example 14 in particular, at pages 92-93, the specification describes the introgression of the GG25 and GJ11 transformation events into elite inbreds and hybrids of maize. In these studies, the GG25 and GJ11 transformation events were each introgressed by backcrossing into the elite inbred lines FBLL (U.S. Patent Appl. No. 08/181,708, filed January 14, 1994) and NL054B (U.S. Patent Appl. No. 08/595,549, filed February 6, 1996). Numerous different plants containing the transgenes were produced over each backcross generation.

Two exemplary hybrids that contained these events were also produced, designated DK626 and DK580. DK580 hybrids were produced by a cross of FBLL to MBZA (U.S. Pat. Appl. No. 08/182,616, filed January 14, 1994) and DK626 hybrids were produced by a cross of NL054B by MM402A (U.S. Pat. Appl. No. 08/181,019, filed January 13, 1994), thereby yielding hybrids containing the respective transformation events. The hybrids were field tested for yield and other agronomic characteristics as well as herbicide tolerance. In Example 12, at pages 90-91 of the specification, it was shown that the hybrids produced exhibited male sterility upon application of glyphosate at the V8 stage of glyphosate application (FIG. 8B), but not during earlier stages of development, when pollen was less fully formed; *e.g.*, at the V4 stage of application (FIG. 8A).

The data in the specification demonstrates the invention of glyphosate-inducible male sterility, which is utilized in the instantly claimed method of plant breeding. A method for generating glyphosate-inducible male sterility is described in the specification, for example, at pages 78 and 79. As described, engineering expression of glyphosate-resistant EPSPS in vegetative tissues, but little or no expression in male reproductive parts, yields a plant capable of being rendered male-sterile by treatment with glyphosate and is vegetatively and female reproductively tolerant to glyphosate.

Glyphosate-inducible male sterility as described in the specification has been confirmed by studies carried out at Monsanto Company, the parent company of the instant assignee, DeKalb Genetics Corporation. As set forth in the Declaration of Dr. Paul C.C. Feng, attached herewith as **Exhibit 1**, histological studies in transgenic maize demonstrated that glyphosate arrests the maturation of microspore pollen cells, resulting in inviable pollen and male sterility. The studies indicated that the impact of glyphosate was focused during the development of

pollen; specifically during the development of the microspore mother cell, tetrad, and microspores. [EXHIBIT 1, paragraphs 5-6]. These studies also demonstrated that pollen with little or no expression of a glyphosate-resistant EPSPS transgene is susceptible to glyphosate, whereas pollen expressing high levels of resistant EPSPS is not. In particular, immunolocalization studies showed that male fertile glyphosate-resistant plants display high expression of glyphosate-resistant EPSPS expression in the tapetum, microspore mother cell, tetrad and microspores, whereas plants exhibiting vegetative glyphosate tolerance and male reproductive intolerance (glyphosate-inducible male sterility), display low to no expression in the same tissues. [EXHIBIT 1, paragraph 6]. Applicants have fully described the invention in the specification. As indicated, all that is required is that minimal expression of an EPSPS transgene be achieved relative to vegetative tissues. Dr. Feng's results confirm the general applicability of the invention.

With regard to the breeding steps set forth in claim 83, Applicants fully describe these, for example, at pages 73-77 of the specification. Described are specific examples of breeding protocols within the scope of the claims. In addition to methods for the production of hybrid corn seed using inducible male-sterility, types of inbred parent lines are also described, such as male and female parents that are elite and derived from different heterotic backgrounds, and into which one or more appropriate transformation events have been backcrossed.

Techniques for fertilization are also described in the specification, including natural or mechanical techniques. Natural pollination occurs in corn when wind blows pollen from the tassels to the silks that protrude from the tops of the incipient ears, whereas artificially directed pollination can be effected either by controlling the types of pollen that can blow onto the silks or by pollinating by hand. Further given are examples of different developmental stages for

glyphosate treatments. Still further provided are descriptions of how rows are planted and harvested. Techniques for applying herbicides, including glyphosate, are also given at pages 20-25 of the specification.

With regard to MPEP §2163, cited in the Action on page 4, Applicants note that the standards given there for the written description requirement confirm the possession of the invention by Applicants. As set forth in MPEP §2163.02, the standard for determining written description is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Citing Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (*quoting In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983)). The substantial evidence presented herein above more than adequately demonstrates full compliance with this requirement.

In view of the foregoing, Applicants respectfully request the removal of the rejection under 35 U.S.C. §112, first paragraph.

F. Rejections Under 35 U.S.C. §112, First Paragraph - Enablement

The outstanding office action rejects claims 83-87 and 96-99 under 35 U.S.C. 112, first paragraph, as not being enabled by the specification. In particular, it is stated that enablement has not been provided for methods of plant breeding comprising use of any inducible male sterile plants comprising an EPSPS transgene. Applicants respectfully traverse.

In response, Applicants first note that the Declaration of Dr. Paul C.C. Feng has been submitted herewith demonstrating the enablement of the claims. [EXHIBIT 1] In the declaration, the success of generating glyphosate-inducible male sterility, as described in the specification, for example, at pages 78 and 79, is confirmed. Dr. Feng's studies confirmed that

glyphosate arrests the maturation of microspore pollen cells, resulting in inviable pollen and male sterility. The impact of glyphosate was focused during the development of pollen; specifically during the development of the microspore mother cell, tetrad, and microspores. [EXHIBIT 1, paragraphs 5-6]. These studies also demonstrated that pollen with little or no expression of a glyphosate-resistant EPSPS transgene is susceptible to glyphosate, whereas pollen expressing high levels of resistant EPSPS is not. [EXHIBIT 1, paragraph 6] In particular, immunolocalization studies showed that male fertile glyphosate-resistant plants displayed high expression of glyphosate-resistant EPSPS expression in the tapetum, microspore mother cell, tetrad and microspores, whereas plants exhibiting vegetative glyphosate tolerance and male reproductive intolerance (glyphosate-inducible male sterility), display low to no expression in the same tissues. [EXHIBIT 1, paragraph 6]. As set forth in paragraph 5 of the Declaration, the results demonstrate that the description of the invention in the specification is correct and enabled.

The studies set forth in Dr. Feng's Declaration show the broad enablement of the claims. As set forth therein, *de novo* creation and analysis of transgenic plants having a glyphosate-inducible male sterile phenotype was demonstrated in multiple independent transformation events. In one study, five independent transformation events were obtained exhibiting inducible male sterility, three of which showed complete inducible sterility. [EXHIBIT 1, paragraph 7]. The events comprised an expression-optimized CaMV 35S promoter upstream of an EPSPS transgene from *Agrobacterium tumefaciens* linked to a non-translated leader sequence from *Petunia hybrida* (hsp70). The five events were backcrossed (2x) into 4 different genotypes (87DIA4, LH59, LH195, and LH198). Acceptable glyphosate-inducible male sterility was observed for all five events transferred into the 87DIA4, LH195 and LH198 background. In an

LH59 background, 4/5 events showed acceptable male sterility from V10/0.56 lb/a. The corresponding treatments for the control were all fertile. Greenhouse evaluations of plants at the R0 stage also showed good male sterility in other backgrounds, including FBLL, LH172, LH244, and LH295. [EXHIBIT 1, paragraph 7]

Dr. Feng's Declaration also describes numerous other plants prepared that exhibited inducible male sterility. In particular, plants were prepared using the constructs in Table 1, resulting in inducible male sterility. The results obtained demonstrate that glyphosate-inducible male sterility works in multiple genotypes. While not every EPSPS event exhibits inducible male sterility, all that is relevant is that such plants can be prepared without undue experimentation. As concluded by Dr. Feng, the specification is enabling for many different combinations of promoters and glyphosate resistant EPSPS transgenes without undue experimentation.

With regard to the statement in the Action that the claims are enabled only for "maize lines" GG25 and GJ11, Applicants again respectfully note that GG25 and GJ11 are transformation events not maize lines. As is described in the specification, these events may readily be transferred by plant breeding techniques including, for example, backcrossing, into other maize plant backgrounds. Accordingly, enablement is not limited to any given plant line. The GJ11 and GG25 events alone are therefore more than adequate to satisfy the enablement requirement.

In this regard, Applicants note that enablement can be provided by the working examples. Example 14, at pages 92-93 of the specification, describes the introgression of the GG25 and GJ11 transformation events into elite inbreds and hybrids of maize. As set forth above, the GG25 and GJ11 events were each introgressed into elite inbred lines. Using the inbred lines,

hybrid varieties were produced that contain these events and were demonstrated to posses the inducible male-sterility trait. The working examples therefore demonstrate full enablement of the claims.

It is finally noted that the legal standard for enablement does not require that Applicants demonstrate enablement for all possible claimed iterations. Enablement must bear only a reasonable relationship to the scope of the claims. *In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). This is echoed in the MPEP: "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). In view of this standard and the substantial evidence presented herein above, Applicants respectfully submit that the full scope of the claims has been enabled. Removal of the rejection under 35 U.S.C. §112, first paragraph is thus respectfully requested.

G. Rejections Under 35 U.S.C. §103(a)

Claims 83-87 and 96-99 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Fabijanski *et al.* (US Pat No. 5356799) in view of Dhingra (US Pat No. 4,735,649). In particular, the Office Action states that Fabijanski teaches a method of plant breeding comprising transforming a plant with an EPSPS gene and "using said transformed plant in a method of plant breeding wherein glyphosate is used to produce male sterility in the female parent." It is further stated that Dhingra teaches a method of producing male sterile plants using glyphosate in a process of breeding. Applicants respectfully traverse.

The cited references do not teach the instantly claimed method and pertain to fundamentally different techniques. The portion of Fabijanski cited in the Office Action, Col. 5, lines 44-59, refers to the use of herbicide resistance genes that are genetically linked to male sterility genes. This is ***not*** inducible male sterility as required by the claims. This is merely the use of a selective agent to select plants having the linked male sterility gene. What the Action has not cited is the portion of Fabijanski in the same paragraph and immediately preceding this, in Col 5, lines 33-44. The citation has been taken out of context. The portion of Fabijanski immediately preceding the cited portion reads as follows:

> According to another aspect of the preceding method as claimed in the claims, we provide a method of increasing the production of seed of the genic male sterile line by transforming the plant of interest with an **antisense gene that is linked to a gene that confers resistance to a selective agent**. According to this scheme, it is possible to produce a male sterile line by crossing the genetically transformed plant (male sterile) with a suitable non-transformed male fertile plant and **using said selective agent to select for plants containing the antisense gene** among plants grown from seed produced from such a cross. (emphasis added)

This section makes clear that Fabijanski refers to a fundamentally different technique than that claimed. Fabijanski involves a method for increasing the production of seed using an antisense gene that is genetically linked to a gene that confers resistance to a selective agent. The plant is not being rendered male sterile by the selection agent. Thus linkage disequilibrium is simply being used to select for linked transgene elements using a selectable marker gene. There has, therefore, been no teaching of the element of a first parent plant that comprises an EPSPS transgene and is capable of being rendered male-sterile by treatment with glyphosate, wherein the plant is vegetatively and female reproductively tolerant to treatment with the glyphosate.

Dhingra does not cure this defect. This reference refers to a gametocide that is a derivative of glyphosate. The reference does not refer to transgenic maize plants that are

vegetatively or female reproductively tolerant to glyphosate. Indeed, Applicants note that in 1985 when the Dhingra application was filed, it was still several years before even the first fertile transgenic maize plant was produced. In contrast, the instant claims require in step (i):

> (i) planting in pollinating proximity seeds capable of growing into first and second parent maize plants, said first parent maize plant **comprising a first EPSPS transgene**, wherein said first parent plant is **capable of being rendered male-sterile** by treatment of said plant with glyphosate, and wherein said first plant is **vegetatively and female reproductively tolerant to said treatment with the glyphosate**;

(Emphasis added) Further, step (iii) of the claims requires:

> (iii) causing said first parent maize plant to be male-sterile by **treating said first parent plant** with said glyphosate; (emphasis added)

Therefore, unlike the prior art, the instantly claimed method involves using a plant that exhibits glyphosate-inducible male sterility, yet is vegetatively and female reproductively tolerant to glyphosate, and treating the plant with glyphosate to induce male sterility. This allows treatment of the entire plant with a glyphosate application that would otherwise kill the plant. This represents a major advance in the art because glyphosate is highly toxic to maize plants. The invention nonetheless allows use of an application of glyphosate in an amount capable of inducing complete male sterility, but that does not harm the vegetatively and female reproductively tolerant plant.

Neither cited reference teaches or suggests a plant that is capable of being rendered male-sterile by treatment with glyphosate while also exhibiting vegetative and female reproductive tolerance to glyphosate. All elements of the claimed invention have thus not been shown to exist in the prior art. In order to support an obviousness rejection, the Examiner must show that the prior art teaches or suggests all claim elements. *See In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991), *see also*, M.P.E.P. § 2142. There must further be a reasonable

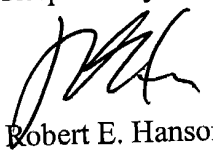
expectation of success. Without teaching all elements of the claims, these elements are missing. Still further, no reasonable motivation or suggestion in the cited prior art or in the knowledge generally available to one of skill in the art to combine any such teachings, had they even existed, can be supported. None of the elements required for a prima facie obviousness rejection have been satisfied. The Action has, therefore, failed to meet the burden of going forward required to establish a *prima facie* case of obviousness under 35 U.S.C. § 103. *See, e.g., In Re Rhinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976); *see also* M.P.E.P. § 2142.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

H. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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